REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of Claims

With this submission, claims 1-5, 10, 16-22, 24, 28-29, 34-35 are amended. Additionally, claims 6-9, 11-15, 23, 25-27 are canceled, and claims 38-39 are newly added. Hence, upon entry of this paper, claims 1-5, 10, 16-22, 24, and 28-39 will remain pending and under active consideration. Specific support for claim 38 can be found on page 17 lines 8-9 of the original specification ("Y is DLeu and Z is Gly-NH_2"). Additionally, specific support for claim 39 can be found on page 43, lines 2-7 ("W/O type emulsion is preferably in the range of about 3,000 cp or less, more preferably in the range of about 2,000 cp or less , even more preferably in the range of about 300 to about 2,000 cp, at about 12 to about 25°C.")

II. Claim Rejection- 35 U.S.C. §103- Hyon in view of Hutchinson

Claims 34 and 35 are rejected under 35 U.S.C. § 103 as obvious over Hyon et al. (US 5,100,669) in view of Hutchinson et al.(US 5,889,110). For the reasons below, Applicants traverse the rejection.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their

established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. Hyon Teaches Away From the Claimed Invention

MPEP § 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." Accordingly, where cited art teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection.

The object of the present invention is to increase productivity of the sustained-release composition by stabilizing a W/O emulsion prepared from an aqueous solution containing an active ingredient and a solution of a lactic acid-glycolic acid polymer (see page 2, lines 1-14 and page 73, lines 12-16). Additionally, the object of this invention is accomplished by adding the specific amount of acetic acid into "an aqueous solution containing an active ingredient." The effects of the present invention are supported by Examples 1 and 6 (assessing the increase of the viscosity of the emulsion).

In contrast, Hyon discloses 'a process for preparing polylactic acid type microspheres containing a water soluble physiologically active substance, which comprises preparing a solution of the water soluble physiologically active substance and the polylactic acid uniformly dissolved in a mixed solvent comprising a hydrophillic organic solvent and water or in an organic acid, mixing the solution with a poor solvent which is immiscible with said mixed solvent or organic acid to give an O/O type or W/O type emulsion, and then subjecting the mixture to the solvent evaporation drying." (Hyon column 3, lines 10-20). Specifically,

the method of Hyon is characterized by using "a solution of water soluble physiologically active substance and the polylactic acid uniformly dissolved."

Therefore, the method of Hyon differs from the present invention characterized by mixing an aqueous solution containing an active ingredient with a solution of a lactic acid-glycolic acid polymer in a low water-soluble organic solvent.

Hyon uses a similar method as the one described in the present invention, where an aqueous solution containing an active ingredient is mixed with a solution of a lactic acid-glycolic acid polymer in a low water-soluble organic solvent (See Comparative Example 3, column 8). However, **Table 2 (column 11-12) of Hyon shows that the method cannot provide the desired effects.** Specifically, Table 2 of Hyon shows that the method shows the cumulative elution of cisplatin at 35.4% at day 1, 86.5% at day 3 and 100% at day 7. Thus, Hyon does not have the sustained release properties as described in the claimed invention. Accordingly, Applicants respectfully submit that the rejection is improper and respectfully request that the rejection be withdrawn.

C. Hutchinson Does Not Cure Hyon

Hutchinson does not cure the deficiencies of Hyon. Specifically, in Example 10 of Hutchinson (column 31), microparticles are prepared by using Leuprorelin acetate and co-polyester comprising 78% molar D,L-lactic acid and 22% molar glycolic acid. However, in the process Leuprorelin actetate and co-polyester are dissolved in anhydride-free glacial acetic acid, and the process does not comprise the method of the present invention in which an aqueous solution containing an active ingredient is mixed with a solution of a lactic acid-glycolic acid polymer in a low water-soluble organic solvent. As such, the claimed invention is not obvious over Hyon and/or Hutchinson alone or in combination. Accordingly, Applicants respectfully submit that the rejection is improper and respectfully request that the rejection be withdrawn.

III. Claim Rejection- 35 U.S.C. §112, first paragraph

Claims 1-33 and 36 are rejected under 35 U.S.C. § 112, first paragraph as not being enabled. Specifically, the Office states that the specification is not enabled for (1) "a (stabilized) 'sustained release composition' as presently claimed," (2) "active agents that can be stabilized based on the 1.5 molar amount or more of acid/base thereto" and (3) "WHAT 'an acid or base' is capable of being used."

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). A person of skill in the art would be able to practice the claimed invention using methods within the specification.

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims to include limitations to the compound "5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO: 1)." Additionally, Applicants now recite the use of acetic acid, and the molar amount between "about 1.5 to about 5 times that of the compound." Finally, Applicants limit the claims to a "solution of a lactic acid-glycolic acid polymer in a low water-soluble organic solvent to obtain a W/O type emulsion." Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Claim Rejection- 35 U.S.C. §112, second paragraph

Claims 1-33 and 36 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. Specifically, the Office states that the specification is unclear with the terms: (1) "sustained-release composition," (2) "in a molar amount of 1.5 or more times," (3) "the metes and bounds of the physiologically active agent," and (4) "WHAT 'an acid or base' is capable of being used 'in a molar amount of 1.5 or more times' v. WHAT polymer, and the latters effect on the former." (Office Action, page 15-16)

A. "Sustained-release composition"

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims as suggested by the Examiner. Specifically, Applicants have added the term "W/O type emulsion" as a constituent feature. Applicants note that "a W/O type emulsion" is not a "sustained release composition," but is an intermediate product in the process for preparing the sustained-release composition.

B. "In molar amount of 1.5 or more times"

The Office argues that paragraphs 236 / 240 to leuprolide to acetic acid shows the "exact opposite" of the molar amount ratio claimed. Specifically, the Office states "para 236/240 to 15.5g leuprolide to .6g acetic acid, totaling 16.2g. This example would appear to be showing the exact opposite in terms of molar amount ratio claimed?" (Office Action, page 15). This is incorrect.

The molecular weights of Leuprorelin acetate and acetic acid are 1269.47 and 60.05, respectively. In paragraph 240, there is the description "Leuprorelin acetate (drug content: 97.4%, acetic acid content: 6.0%)" (See paragraph [0240] of the published application or page 67 of the original specification). A molar amount of Leuprorelin is calculated for Leuprorelin acetate as shown below:

[15.5g x 97.4% (drug content)] / 1269.47 (molecular weight of Leuprorelin) = **0.0119 mole**.

Additionally, a molar amount of acetic acid contained in Leuprorelin acetate (15.5 g) described in paragraph 236 is calculated as follows:

[15.5 g x 6% (acetic acid content)] / 60.05 (molecular weight of acetic acid) = **0.155 mole**.

A molar amount of acetic acid contained in "aqueous acetic acid (prepared by dissolving 0.6 g of glacial acetic acid in 31.75 g of distilled water)(16.2 g)" described in paragraph 236 is calculated as follows:

16.2 g x (0.6 g/(0.6 g + 31.75 g))acetic acid content in the above aqueous acetic acid) / 60.05 (molecular weight of acetic acid) = **0.005 mole**.

Therefore, a total molar amount of acetic acid is 0.025 mole (0.0155 + 0.005 = 0.0205 mole). Thus, in paragraph 236, 0.0205 mole of acetic acid and 0.0119 mole of Leuprorelin are used, and the acetic acid / Leuprorelin (mole ratio) is "0.0205 mole / 0.0119 mole = about 1.72"

C. "Physiologically active agent"

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims as suggested by the Examiner. Specifically, Applicants have added the term "5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO: 1) wherein Y represents DLeu, DAla, DTrp, DSer (tBu), D2Nal or DHis (ImBz1) and Z represents NH-C_2H_5 or Gly-NH_2" and removed the term "physiologically active substance."

D. "acid or base" and "polymer"

In an effort to advance prosecution of this application and without acquiescing to the propriety of this rejection, Applicants have amended the claims as suggested by the Examiner. Specifically, Applicants have added a specific compound "5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (SEQ ID NO: 1) wherein Y represents DLeu, DAla, DTrp, DSer (tBu), D2Nal or DHis (ImBz1) and Z represents NH-C_2H_5 or Gly-NH_2." Additionally, as suggested by the Examiner, Applicants have limited the claims to "acetic acid in a molar amount of about 1.5 to about 5 times that of the compound."

For at least the reasons described above, Applicants respectfully request reconsideration and withdraw of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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